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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,185	07/18/2001	C. Frank Bennett	RTS-0258	1505

7590 06/27/2003

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	8

DATE MAILED: 06/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/910,185	Bennett et al
Examiner	**Art Unit**
Jane Zara	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 15, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, 4-10, and 12-15* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 4-10, and 12-15* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office action is in response to the communication filed April 15, 2003, Paper No. 7.

Claims 1, 2, 4-10 and 12-15 are pending in the instant application.

Response to Arguments and Amendments

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Kalff-Suske et al.

Kalff-Suske et al (Document AA, submitted in IDS filed on July 18, 2001, Paper No. 3) teach antisense oligonucleotides between 8-50 nucleobases that specifically hybridize and inhibit the expression of human glioma associated oncogene-3 in vitro (See last paragraph on p. 1775-top paragraph on p. 1776).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-10 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kalff-Suske et al (as applied in the 102 rejection above) and Ruppert et al, the combination in view of Milner et al and Baracchini et al.

The claims are drawn to compositions comprising antisense oligonucleotide compounds between 8-50 nucleotides which specifically target and inhibit the expression of human GLI-3 of SEQ ID NO: 3 in vitro, and which oligonucleotides further comprise a phosphorothioate internucleotide linkage modification, a 2'-O-methoxyethyl sugar modification, a 5-methyl cytosine nucleobase modification, and may optionally comprise a chimeric oligonucleotide, and which compositions further comprise a pharmaceutically acceptable diluent and a colloidal dispersion system.

Kalff-Suske et al is relied upon as cited in the 102 rejection above. Furthermore, Kalff-Suske et al teach the polynucleotide sequence of GLI-3 encoded by SEQ ID NO: 3, as well as mapping of various mutations throughout GLI-3 polynucleotide sequence and their relationship to various craniofacial and limb anomalies associated with Grieg cephalopolysyndactyly syndrome

(See entire document, especially last paragraph on p. 1775-top paragraph on p. 1776; see also accession number AJ250408 and the accompanying sequence alignment data).

Ruppert et al (Document AI, submitted in IDS filed on July 18, 2001, Paper No. 3) teach the polynucleotide sequence encoding GLI-3, of SEQ ID NO: 3 (See entire document, especially figure 2 on page 5410 and the accompanying sequence alignment data).

Neither Ruppert nor Kalff-Suske et al do not teach the in vitro inhibition of GLI-3 expression using antisense oligonucleotides between 8-50 nucleobases, nor the incorporation of any modification into the antisense oligonucleotides, nor compositions comprising pharmaceutically acceptable diluents or colloidal dispersion systems.

Milner teaches methods of designing and assessing the ability of various antisense oligonucleotides to target and inhibit the expression of a target nucleic acid of known nucleic acid sequence in vitro (See entire document, especially figure 1 on p 538).

Baracchini et al teach the incorporation of phosphorothioate internucleotide linkages, 2'-O-methoxy ethyl sugar modifications, 5 methyl cytosines and chimeric structures into antisense oligonucleotides for enhancing target binding, cellular uptake and stability of antisense oligonucleotides, as well as compositions comprising antisense oligonucleotides, pharmaceutically acceptable diluents and colloidal dispersion systems for cellular delivery (see col. 4-14).

It would have been obvious to one of ordinary skill in the art to target and inhibit the expression of GLI-3 in vitro comprising the administration of antisense oligonucleotides between 8-50 nucleobases because Milner teaches methods of designing and assessing antisense

oligonucleotides between 8-50 nucleobases for their ability to target and inhibit the expression of a known target gene in vitro and both Ruppert and Kalff-Suske et al teach the nucleic acid sequence encoding GLI-3 (of SEQ ID NO: 3). One of ordinary skill in the art would have been motivated to utilize such a method of finding optimal antisense oligonucleotides between 8-50 nucleobases which best target and inhibit GLI-3 expression, as taught by Milner et al, in order to study this target molecule's role in various cellular processes, such as craniofacial and limb development because GLI-3's role in development had been taught previously by Kalff-Suske et al, and Ruppert et al have taught an association between amplification of GLI-3 and tumor growth (See Ruppert et al in the abstract and introduction on p. 5408). One of ordinary skill in the art would have been motivated to incorporate various modifications into antisense such as internucleotide linkage, nucleobase, or sugar modifications, as well as designing chimeric antisense oligonucleotides, because Baracchini had taught previously that such modifications contribute to the stability, cellular uptake and target binding of antisense oligonucleotide compounds. One of ordinary skill in the art therefore would have expected that antisense comprising such modifications would exhibit enhanced stability, cellular uptake and target binding. One of ordinary skill in the art would have been motivated to utilize compositions comprising pharmaceutically acceptable diluents and colloidal dispersion systems, in combination with antisense oligonucleotides, for transfecting target cells because such compositions had been taught previously by Baracchini et al and one would have expected that such compositions would minimize toxic effects of target cells while enhancing cellular uptake of the antisense

oligonucleotides. Therefore, the invention has a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

June 24, 2003

Karen Lacourciere

KAREN LACOURCIERE
PATENT EXAMINER